DNA Damage

DNA Damage ⟶ mutation

↓

Repaired by Repair System

if any Damage escape from repair. Then damage become permanent = K/a Mutation

Mutated cells

- Apoptosis → PCD
- Senescence [irreversible Dormant]
- melignent → Cancerous

⇒ Type of mutation

* Single Nt. mutation

① Base Substitution

eg- Sickel cell anemia ✓

6th codon of β-Globin chain: GAG ⟶ (Transversion) GUG

GAG → Glu (-ve)

GUG → Val = 0

β-chain of Hb is changed in Conformation

↓

RBC Sickel Shape

↓

Sickel cell anemia

Purine ⇌ Pyrimidine

Base Substitution

(a) Transition

Purine ⟶ Purine

Pyrimidine ⟶ Pyrimidine

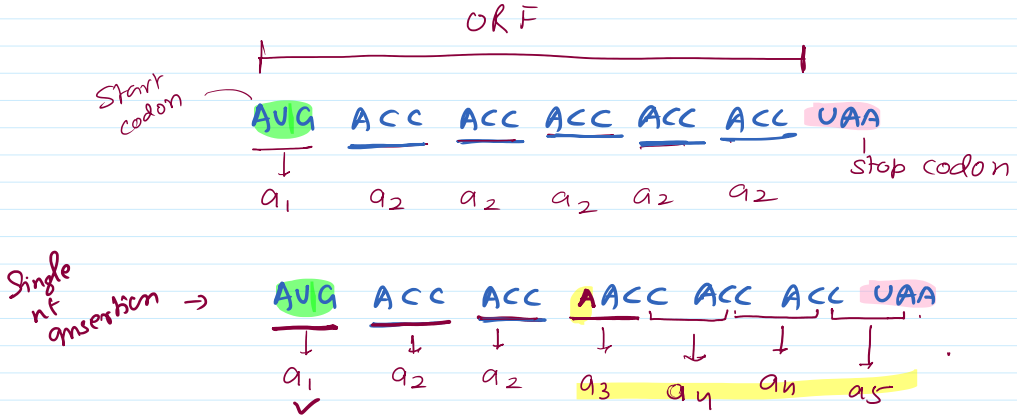
(b) Transversion (more harmfull mutation)

Purine ⇌ Pyrimidine

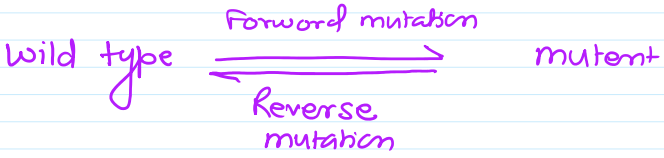
② Insertion or deletion

- Single nt or Double nt insertion or deletion is more harmfull than 3 nt insertion or deletion

Reason - single nt insertion/deletion can cause frame shift mutation

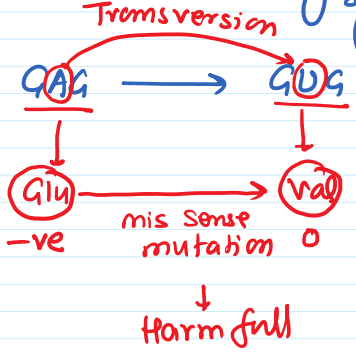


Forword mutation →



Mis-Sense mutation

Change in nt → older a.a. is replaced by New a.a. which is of different Nature



Non-Sense mutation

- Normal codon is replaced by stop codon

↓

K/a non sense mutation

↓

Can produce Truncated Protein

Nutral mutation (conserve mutation)

Change in Nt → Change in codon

↓

Change in a.a.

- a.a. is replaced by same Nature of a.a.

Glu ⟶ Asp
(-ve) (-ve)

Lys ⟶ Arg
(+ve) (+ve)

Silent mutation / Same Sense mutation (Conserve)

* 1 a.a. Can be coded by more than 1 codon

if There is change in Nt. → change in codon

↓

a.a. remain same

Other mutation –

Gain of function- New trait appeared in inappropriate tissue in inappropriate time

Loss of function- Compleat or partial loss of a phenotype

Leathal mutation- Premature Death

Cause of mutation

Endogenous Factor

- Error in Replication (mis match)
- oxidation damage due to ROS
- Hydrolytic Cleavage
- Spontanious deamination
- Spontanious depurination

Exogenous Factor

Chemical Agent

- → Alkylating Agent
- → Cross Linker
- → Inter calating agent
- → Base Analog

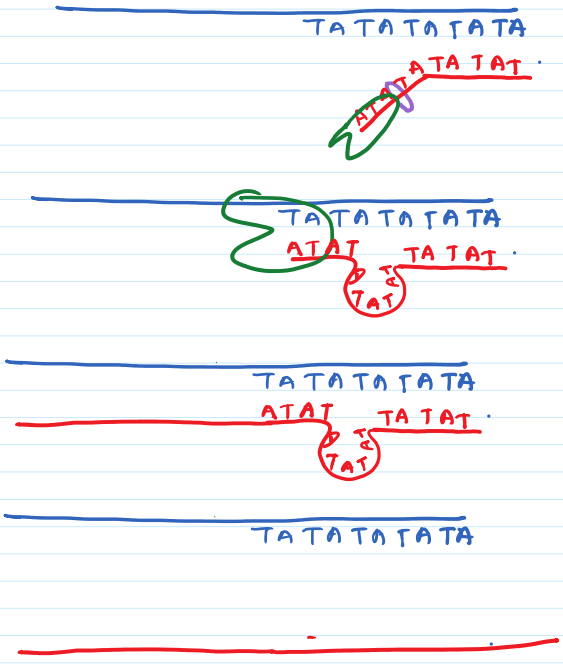
Physical Agent

- Ionizing Radiation
- Non ionizing Radiation

Endogenous Source of DNA Damage-

① Error in DNA Replication

- Base Substitution (Transition or Transversion)
- Slippage error at telomeric End
  - ↓
  - Use of No. at telomeric End



(2) Topoisomarase mediated DNA Damage

↳ Remove Superhelical str.

Topo·I → Nicked DNA Rotation & Rescaling

↓

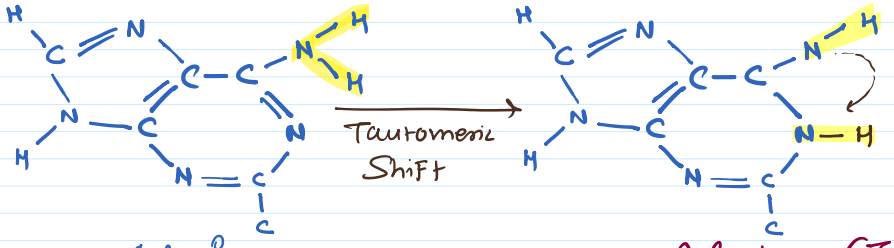
Chance of mutation

(3) Transposon

- Can Insert in a functional gene Randomly and can cause Insertional inactivation of a gene

(4) Tautomeric Shift in DNA bases-

Shifting of H Atom / Rearrangement of H Atom with in Nitrogenous base



Adenine (Amino form)

Adenine (Imino form)

Adenine & Cytosine [Amino form] NH_2 ✓ H- Doner

Tautomeric Shifting → A* & C*

Imino form [NH] (H- Acceptor) ✓

Thymine & Guanine (keto form) C=O ✓ H- Acceptor

Tautomeric Shifting → T* & G*

Enol form (C-OH) ↓ H- Donor

Nitrogenous Base Pairing

Amino – A = T

A* = C

Keto. – G ≡ C

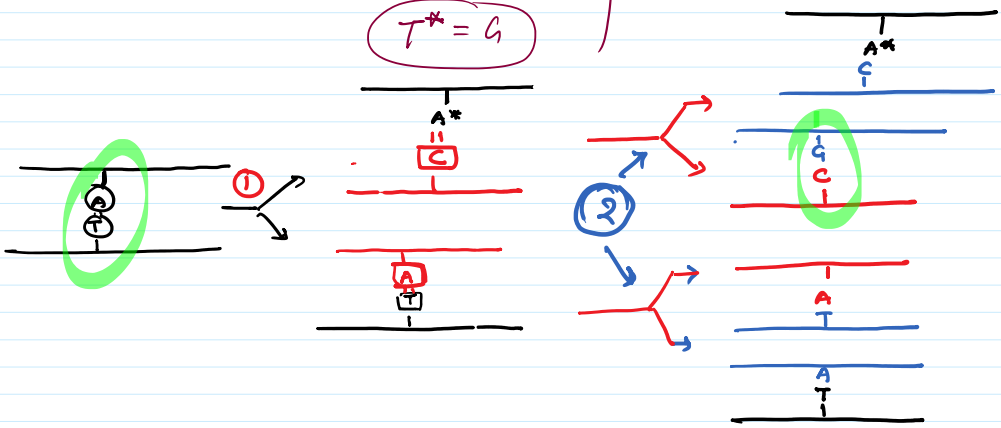
G* = T

Amino C ≡ G

C* = A

Keto T = A

T* = G



Purine → Purine

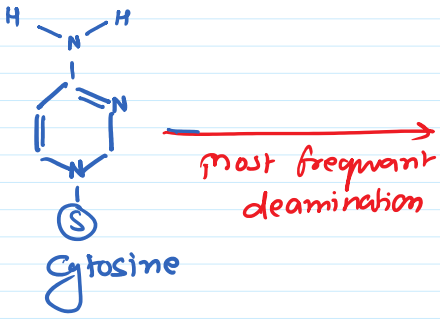
A → G

T → C

Pyr → Pyr

Transition

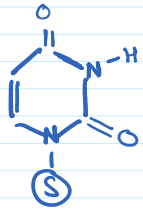
(5) Spontanious Deamination



Cytosine

(Pyrimidine)

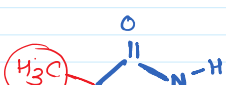
most frequent deamination

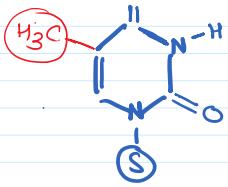


Uracil

Pyrimidine

Transition





5 methyl Uracil (Thymine)

C → U (NH2)

A → Hypoxanthin (Hx) [Hx ≡ C | NH2 ↔ A = T]

Hx ≡ C

G → Xanthine (NH2)

G ≡ C

A → G
‖ ⫼
T → C

↓

Transition

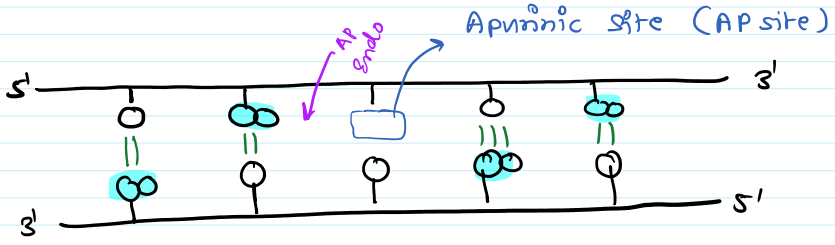
(6) Spontanious depurination

Bulky Nitrogenous moiety = Purine

↓

Double Ring str.

Purine loss is most Common



* AP site is recognized by AP Endonuclease endnuce cut on 5' end of AP site

↓

Repaired by Base Excision Repair System

* AP Site Can by pass through TLS Polymarase

(7) Oxidative DNA Damage

Reactive oxygen Sp. [ROS] → produced in cell

ROS → Nutilized in cell

Stress ↑ = ROS ↑

$[O^-]$, $[O_2^-]$, $[H_2O_2]$, OH^-

↓

Oxidative Damage

Guanine → 8-oxo-Guanine

G ≡ C

8-o-G- = A

↓

G ≡ C → T = A

T = A

Trans version (Harmfull)

⑧ DNA methylation

S-adenosyl metheonine [SAM]

G → N^7 methyl Guanine (most common)

Ⓐ → N^3 " Adenine

Ⓖ → O^6 " Guanine (Rare)

Exogenous Source of DNA Damage.

- Chemical agent
- Physical agent

Exogenous Source of DNA Damage

- Chemical Agent
- Physical Agent

(A) Alkylating Agent

- Transfer methyl, ethyl Group

eg - N^7 methyl Guanine
N^3 methyl Adenine

modification Sites for A & G
↳ [N^1, N^3, N^6, N^7]

eg - of Alkylating Agents -

→ methyl, methane Sulfonate [mms]
→ Ethyl methane Sulfonate (EMS)
→ N methyl - N'- Nitro - Nitrosoguanidine [MNNG]

MMS
↓
N^7 methyl Guanine
N^3- " Adenine [produced Apsite]

MNNG & MNU MNU = methyl Nitroso urea
↓
G → O^6 - methyl Guanine

G ≡ C O^6 - methyl Guanine = T

(G) ≡ (C) (A) = (T)

G ≡ C
↓ ↓
A = (T) Transition

Polycyclic aromatic Hydrocarbons

Cyt P450 Enzyme
↓
Aflatoxin (inactive) Aflatoxin (Active)

Other Alkylating Agents →

Sulfur & Nitrogen mustered

↓

K/A mustered Gas

↓

Block DNA Protein interaction

Aromatic amines

eg - 2 amino purine

↓

N-acetyl-2-amino flourene [AAF]

↳ (Carcinogenic)

Cyt P450

Aromatic amines

Carcinogenic Alkylating agents

* Polycyclic aromatic Hydrocarbon -

eg - Benzopyrine = major Cancer Risk

↓

tnt in Cigrette Smoke

* Toxin → Aflatoxin (most potent carcinogen for liver cell)

↓

derived from Aspergillus parasiticus

Base Analogus

↳ incorporated in DNA during Replication

eg - 5-Bromouracil → Artificial Analogue of T

2 Aminopurine → " " " A

5-methyl Uracil → Natural " " T

Bu = A

(keto)

↓ | Transition

BU* = G

(Rare)

Intercalating Agents

- Contain polycyclic Ring str.

eg- Proflavin, acridine, ethidium bromide

- Binds to major & minor groove of DNA
- induce 18° +ve turn
- Positive Supercoiling
- Can cause frame shift mutation

During Replication in New DNA Strand Extra nt added infront of intercalating agent → cause frame shift mutation

Physical Agents

Ionizing Radiation

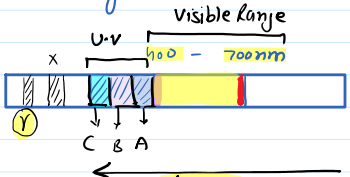
also k/a Clastogens

- Induce SS break / Ds Break

eg- α, β, γ & x Ray's

Non-ionizing Radiation

- U.V. Rays

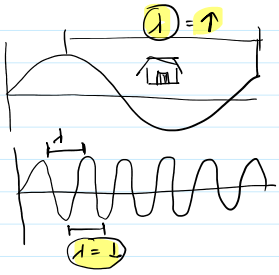


λ = ↓

ε = ↑

λ = ↑ & ε ↓

$O_2 \xrightarrow{U.V.C} O_3$

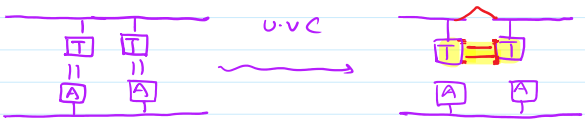


- U.V.C = 190nm - 290 nm
- U.V B = 290 - 320 nm

→ Ozone layer

U.V.A = 320 - 400 nm → Reached on Earth

* U.V.C = Can cause Cyclobutane dimer formation in DNA



⇒ Pyrimidine dimer

↳ TT > TC > CT > CC
75%

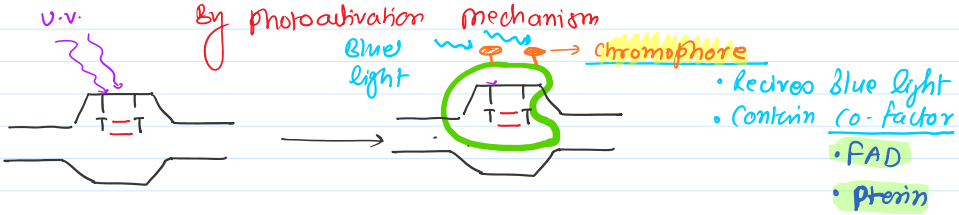
⇒ DNA Repair

1. Direct Repair
   - (i) Photoactivation (Photolyase)
   - (2) methyl Transferase / Alkyl Transforase
2. Excision Repair
   - (i) mismatch Repair
   - (ii) Nt Excision Repair
   - (iii) Base Excision Repair
3. SOS Repair
4. Double Strand Break Repair
5. Single Strand Break Repair

1 Direct Repair

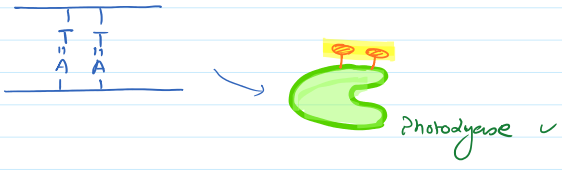
(i) Photolyase
↳ involve in Direct Repair

By photoactivation mechanism



- Recives Blue light
- Contain co-factor
  - FAD
  - Protein

→ when Chromophore Recives Blue light Photolyase become active & Resolve Cyclobutane Ring Str.



(ii)

2 Alkyl Transferase / methyl Transferase